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A POPULATION-BASED ANALYSIS OF PATIENT AGE AND
OTHER DISPARITIES IN THE TREATMENT OF OVARIAN CANCER
IN CENTRAL APPALACHIA AND KENTUCKY

THESIS

A thesis submitted in partial fulfillment of the
requirements for the degree of Master of Science in Clinical Research
Design in the College of Public Health
at the University of Kentucky

By

Robert Martin Ore

Lexington, Kentucky

Director: Dr. David Mannino, Professor of Medicine

Lexington, Kentucky

2019

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ABSTRACT OF THESIS

A POPULATION-BASED ANALYSIS OF PATIENT AGE AND OTHER DISPARITIES IN THE TREATMENT OF OVARIAN CANCER IN CENTRAL APPALACHIA AND KENTUCKY

Objectives: Adherence to National Comprehensive Cancer Network (NCCN) guidelines for ovarian cancer treatment improves patient outcomes. The aim of this study is to assess disparities associated with ovarian cancer treatment in the state of Kentucky and Central Appalachia.

Methods: Patients diagnosed with ovarian cancer from 2007-2011 were extracted from administrative claims-linked Kentucky Cancer Registry data. NCCN compliance was defined by stage, grade, surgical procedure and chemotherapy. Selection criteria were carefully reviewed to ensure data quality and accuracy. Descriptive analysis, logistic regression, and Cox regression analyses were performed to examine factors associated with guidelines compliance and survival.

Results: Most women were age 65 years or older (62.5%), had high grade (65.9%) and advanced stage (61.0%) ovarian cancer. Two-thirds of cases (65.9%) received NCCN-recommended treatment for ovarian cancer. The hazard ratio (HR) of death for women who did not receive NCCN-compliant care was 62% higher compared to the women who did receive NCCN compliant treatment (HR 1.62, 95% CI 1.11-2.35). Results from the logistic regression showed that NCCN-compliant treatment was more likely for: women age 65-74 years compared to age 20-49 (OR=3.32, 95% CI=1.32-8.32), late stage compared to early stage cancers (OR 0.32, 95% CI 0.20-0.53), receipt of care at tertiary hospitals (OR=1.92, 95% CI=1.10-3.34), and privately insured compared to Medicaid (OR=0.31, 95% CI=0.13-0.77) or Medicare (OR=0.31, 95% CI=0.15-0.66).

Conclusions: When the treatment of ovarian cancer did not follow NCCN-recommendations, patients had a significantly higher risk of death. Women were less likely to receive NCCN-compliant care if they were of younger age (20-49 years), had early stage disease, were not privately insured, or had care provided at a non-tertiary hospital.

Keywords: NCCN Guideline Compliance, Ovarian Cancer, Healthcare disparities

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15DEC2018

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HIGHLIGHTS

- There is a higher risk of death if ovarian cancer treatment is not NCCN-compliant
- Younger women are more likely to receive non-compliant care than older women
- Non-compliance was also more common for early stage disease and non-private insurance

CHAPTER 1. INTRODUCTION

Ovarian cancer is one of the more lethal gynecologic cancers as it regularly presents in advanced stage (1) and many women do not receive expert-recommended care (2). Until progress is made with the early detection of ovarian cancer, it is important to understand the barriers preventing women from receiving NCCN-compliant treatment. The National Comprehensive Cancer Network (NCCN) publishes detailed guidelines for the treatment of ovarian cancer which include comprehensive surgical staging for early stage cancers and aggressive surgical cytoreduction for advanced stage disease. With the exception of low grade early stage ovarian malignancies, platinum and taxane-based chemotherapy is recommended following surgery. Adherence to NCCN guidelines has been shown to improve patient outcomes (2). Unfortunately, as many as two-thirds of women with ovarian cancer are not referred to a gynecologic oncologist for their primary surgery (3) (4) and a similar fraction do not receive NCCN-compliant care (2).

A number of factors have previously been associated with non-compliant treatment according to NCCN guidelines. These include hospital and surgeon case volume (2), treatment at NCI Comprehensive Cancer Center facilities (5), cancer stage (6), geographic proximity to the hospital (7), race (8), and socioeconomic status (8). Even though the median age at diagnosis for ovarian cancer is 63 years, 55% of women diagnosed with invasive ovarian cancer are younger than 65 years of age (9); therefore, women of all ages should be included in population-based evaluations. We should also consider whether non-compliant treatment is an intentional act of commission. A single institutional report from the University of Alabama at Birmingham noted that common reasons for non-compliance were intentional and related to: chemotherapy toxicity,

disease progression, patient refusal, and co-morbidities preventing recommended surgery or chemotherapy (10). An analysis of guideline concordance for colorectal cancer in the Appalachian region of Kentucky demonstrated that non-compliance was associated with chronic medical conditions, including myocardial infarction and congestive heart failure; and surgical non-compliance was associated with low volume centers and hospitals that were not designated by the Commission on Cancer (COC) (11).

Our study objective was to perform a detailed analysis of treatment disparities for ovarian cancer in the state of Kentucky and Central Appalachia based on published NCCN guidelines.

CHAPTER 2. MATERIALS AND METHODS

This is a retrospective, population-based investigation of women diagnosed with ovarian cancer while living in the state of Kentucky from January 1, 2007 to December 31, 2011. Permission to perform the investigation was granted by the University of Kentucky Institutional Review Board as an exempt protocol.

Ovary cancer cases were selected based on ICD-O-3 site codes C569, and extracted from the Kentucky Cancer Registry (KCR) database. The KCR database was linked to insurance claim databases in the state of Kentucky including Medicare, Medicaid, and private insurers. This unique merging of clinical data eliminated patient age constraints seen when cancer registries are coupled to Medicare (patients age 65 years and older). In addition, use of both private and non-private insurers allow for a more complete review of medical comorbidities and insurance-related variables.

Patient eligibility included an ovarian cancer diagnosis in the state of Kentucky, age over 20 years, and a first diagnosis of an invasive cancer. To ensure complete and accurate treatment information, we included only patients with continuous insurance enrollment in the first year of cancer diagnosis (month of cancer diagnosis and 12 months following) or till the month of death in the first year. Borderline and non-epithelial ovarian malignancies were excluded from this study. There were 1,450 cases identified with a diagnosis of ovarian cancer during the study period. Three hundred and sixty-one cases were excluded, as they had insufficient details to determine surgical procedures performed. Twenty were excluded due to age under 20 years, and 179 were excluded as ovarian cancer was not their first cancer diagnosis. An additional 68 cases were excluded due to non-epithelial histology. Since we defined NCCN-compliance to include

chemotherapy information captured from KCR linked claims files, 322 cases were excluded as they did not have at least 13 months of continuous claims data. Thus, there were a total of 413 cases for the complete analysis.

The primary outcome investigated was compliance with NCCN recommendations for ovarian cancer treatment. Chemotherapy and surgical guideline compliance were grouped together to form a single bivariate value for compliance. For stages IIIB and below, adherence required a minimum performance of oophorectomy and lymphadenectomy, whereas stages IIIC and above required a minimum of oophorectomy and omentectomy, and allowed for more extensive cytoreductive procedures. Guideline compliance required chemotherapy administration for all study cases with the exception of stage IA and stage IB grade 1 cancers. Surgical information was captured using KCR data, and chemotherapy information was identified by claims data linked to KCR data.

Hospitals were classified as high volume (>15 cases per year) or low volume (<15 cases per year) based on the number of ovarian cancer cases performed. Academic hospitals were defined to be tertiary hospitals. The patient-specific variables analyzed were: age, race, insurance type, Appalachian residence versus metropolitan status, educational level (percentage with high school education at county level), income level (percentage below the poverty level at county level), insurance type, treatment with neoadjuvant chemotherapy, and geographical distance to the closest tertiary hospital. We used the Great Circle Distance (GCD) method to calculate geographical distance, adapted North American Association of Central Cancer Registries (NAACCR)'s SAS application (GIS Resources. *NAACCR* <https://www.naaccr.org/gis-resources/#GREATCIRCLE>). Appalachian status was based on the definition from the Appalachia Regional

Commission (<https://www.arc.gov/index.asp>). The 2003 Rural-Urban Continuum Codes were used to define metro and non-metro status with values 1-3 as metro and 4-9 as non-metro <https://www.ers.usda.gov/data-products/rural-urban-continuum-codes/>. The Charlson Comorbidity Index (CCI) was assigned based on KCR linked claims data from a time period spanning 12 months to one month prior to cancer diagnosis. The CCI variable was treated as unknown when 12 months of continuous claims coverage prior to the cancer diagnosis was unobtainable. Tumor-related variables included: cell type, stage, grade, number of lymph nodes examined, and tumor size.

Descriptive analysis was conducted for all variables. Bivariate analyses with Chi-Square tests were performed to examine the association between guideline compliance and other covariates. Multivariate logistic regression models were fitted to determine significant factors associated with the delivery of NCCN-compliant care. Kaplan-Meier plots and Log-Rank tests were conducted for survival analysis. A Cox regression analysis was performed to determine the survival effects of various covariates, including NCCN compliance. All analyses were done using SAS Statistical software version 9.4 (SAS Institute, Inc., Cary, NC). Statistical tests were two-sided with a p -value ≤ 0.05 used to identify statistical significance.

CHAPTER 3. RESULTS

Two hundred and seventy-two women out of a total study population of 413 (65.9%) received NCCN guideline compliant care. For the 141 women who did not receive guideline-compliant care, 87 (61.7%) did not receive the recommended chemotherapy, and 79 (56.0%) did not receive the appropriate surgery.

The summary of demographic characteristics is shown in Table 1. The mean age of the study population was 65.5 years, and 62.3% of study subjects were 65 years or older. More than half of the cancers were diagnosed at an advanced stage (60.9%). The majority were also grade 3 or 4 malignancies (65.7%). Fewer than 10% of patients had a Charlson Comorbidity Index greater than 2. Only 39.1% of cases were treated at a tertiary hospital, while 58% were treated at high volume hospitals as defined by at least 15 ovarian cancer cases per year. Medicare insured 65% of the women in this study. Although more women were treated in non-Appalachian metropolitan areas (44.7 %) than any other, 31.2% were still treated in rural Appalachia.

3.1 NCCN Guideline Compliance

The bivariate analysis between patient characteristics and NCCN-compliance are listed in Table 1. Women who received NCCN-adherent care were more likely to have late stage disease (stage III and stage IV), smaller size tumors (less than 10 cm), and treatment at a tertiary hospital. Women from non-Appalachian metropolitan areas were more likely (51.9%) to have private insurance carriers, whereas women from Appalachian rural areas were more likely to be covered by Medicaid. Patient income and education level were not associated with NCCN compliance or survival. The average

Great Circle Distance (GCD) to the closest academic hospital for all subjects was 62.9 miles (± 48.5 miles). The average GCD for non-compliant cases GCD was 59.8 miles (± 45.3 miles) compared to NCCN-compliant cases of 64.5 miles (± 50.1 miles). There was no statistical difference between these groups.

The characteristics associated with NCCN guideline adherence on multivariate logistic regression are shown in Table 2. Women of age 65-74 years were significantly more likely to be guideline compliant compared to women age 20-49 years (OR 3.316, 95% CI 1.322-8.320). Compared to stage IIIC and IV, treatment of earlier stage disease was less NCCN-compliant (OR 0.32, 95%CI 0.198-0.526). Patients treated at a tertiary hospital were also more likely to receive NCCN-adherent care (OR 1.921, 95%CI 1.104-3.341). Compared to women who were privately insured, those insured by Medicaid (OR 0.311, 95%CI 0.125-0.774) or Medicare (OR 0.312, 95%CI 0.148-0.659) were much less likely to be guideline compliant.

3.2 Patient Survival

The results from the Cox regression model are shown in Table 3. NCCN guideline compliant treatment was associated with significantly better survival (HR=1.615, 95%CI 1.111-2.347) than non-compliant cases. In addition, women who lived in non-Appalachian metropolitan areas had better survival compared to women living in rural Appalachian areas (HR 0.698, 95%CI 0.491-0.990). Patient's distance to closest tertiary hospital was marginally associated with survival (HR 1.003, 95%CI 1.000-1.006). As expected, overall survival was better for younger compared to older women, early compared to late stage diagnosis, and women with low compared to high CCI.

Table 1. Characteristics of Patients with Ovarian Cancer by NCCN Guideline Adherence Status, 2007-2011

| Variables | Total | | Guideline Non-Compliant | | Guideline Compliant | | P value |
|-----------------|-------|-------|-------------------------|------|---------------------|------|---------|
| | N | % | N | % | N | % | |
| Total | 413 | 100.0 | 141 | 34.1 | 272 | 65.7 | |
| Age | | | | | | | |
| 20-49 | 46 | 11.1 | 20 | 43.5 | 26 | 56.5 | 0.121 |
| 50-64 | 109 | 26.3 | 34 | 31.2 | 75 | 68.8 | |
| 65-74 | 163 | 39.4 | 48 | 29.5 | 115 | 70.6 | |
| >75 | 95 | 22.9 | 39 | 41.1 | 56 | 59.0 | |
| Race | | | | | | | |
| White and other | 402 | 97.1 | 138 | 34.3 | 264 | 65.7 | 0.756 |
| Black | 11 | 2.7 | 3 | 27.3 | 8 | 72.7 | |
| Stage | | | | | | | |
| I | 114 | 27.5 | 47 | 41.2 | 67 | 58.8 | 0.000 |
| II | 47 | 11.4 | 23 | 48.9 | 24 | 51.1 | |
| III | 166 | 40.1 | 37 | 22.3 | 129 | 77.7 | |
| IV | 86 | 20.8 | 34 | 39.5 | 52 | 60.5 | |
| Grade | | | | | | | |
| 1 | 23 | 5.6 | 9 | 39.1 | 14 | 60.9 | 0.097 |
| 2 | 64 | 15.5 | 26 | 40.6 | 38 | 59.4 | |
| 3 | 165 | 39.9 | 52 | 31.5 | 113 | 68.5 | |
| 4 | 107 | 25.8 | 29 | 27.1 | 78 | 72.9 | |
| Unknown | 54 | 13.0 | 25 | 46.3 | 29 | 53.7 | |
| Tumor Size | | | | | | | |
| <5 cm | 78 | 18.8 | 23 | 29.5 | 55 | 70.5 | 0.030 |
| 5-10 cm | 100 | 24.2 | 24 | 24.0 | 76 | 76.0 | |
| >10 cm | 148 | 35.7 | 60 | 40.5 | 88 | 59.5 | |
| Unknown | 87 | 21.0 | 34 | 39.1 | 53 | 60.9 | |

Table 1. (continued)

| Charlson Comorbidity Index | | | | | | | 0.216 |
|---|------------|-------------|----|------|-----|-------|-------|
| 0 | 226 | 54.6 | 71 | 31.4 | 155 | 68.6 | |
| 1 | 100 | 24.2 | 34 | 34.0 | 66 | 66.0 | |
| 2 | 20 | 4.8 | 9 | 45.0 | 11 | 55.0 | |
| 3 or greater | 11 | 2.7 | 2 | 18.2 | 9 | 81.8 | |
| Unknown | 56 | 13.5 | 25 | 44.6 | 31 | 55.4 | |
| Tertiary versus Non Tertiary Hospital | | | | | | | 0.048 |
| Tertiary Hospital | 162 | 39.1 | 46 | 28.4 | 116 | 71.6 | |
| Non Tertiary Hospital | 251 | 60.6 | 95 | 37.9 | 156 | 62.2 | |
| Hospital Volume of Ovary Cancer Cases per year | | | | | | | 0.095 |
| > 15 cases/year | 240 | 58.0 | 74 | 30.8 | 166 | 69.2 | |
| <15 cases/year | 173 | 41.8 | 67 | 38.7 | 106 | 61.3 | |
| Income Level | | | | | | | 0.873 |
| Low | 114 | 27.5 | 39 | 34.2 | 75 | 65.8 | |
| Moderate | 103 | 24.9 | 33 | 32.0 | 70 | 68.0 | |
| High | 94 | 22.7 | 31 | 33.0 | 63 | 67.0 | |
| Very High | 102 | 24.6 | 38 | 37.3 | 64 | 62.8 | |
| Insurance Type | | | | | | | 0.068 |
| Not Insured | 3 | 0.7 | 2 | 66.7 | 1 | 33.3 | |
| Private Insurance | 106 | 25.6 | 26 | 24.5 | 80 | 75.5 | |
| Medicaid | 33 | 8.0 | 16 | 48.5 | 17 | 51.5 | |
| Medicare | 269 | 65.0 | 97 | 36.1 | 172 | 63.9 | |
| Other Public | 1 | 0.2 | 0 | 0.0 | 1 | 100.0 | |
| Unknown | 1 | 0.2 | 0 | 0.0 | 1 | 100.0 | |

Table 1. (continued)

| Appalachian Residence Metropolitan Status | | | | | | |
|--|------------|-------------|----|-------|-----|------|
| Appalachian Metro Area | 18 | 4.3 | 2 | 11.1 | 16 | 88.9 |
| Appalachian Rural Area | 129 | 31.2 | 46 | 35.7 | 83 | 64.3 |
| Non Appalachian Metro Area | 185 | 44.7 | 62 | 33.5 | 123 | 66.5 |
| Non Appalachian Rural Area | 81 | 19.6 | 31 | 38.3 | 50 | 61.7 |
| Chemotherapy Adherence | | | | | | |
| Chemotherapy Adherent | 323 | 78.2 | 54 | 16.7 | 269 | 83.3 |
| Chemotherapy Non Adherent | 90 | 21.8 | 87 | 96.7 | 3 | 3.3 |
| Surgery Adherence | | | | | | |
| Surgery Adherence | 334 | 80.9 | 62 | 18.6 | 272 | 81.4 |
| Surgery Non Adherence | 79 | 19.1 | 79 | 100.0 | 0 | 0.0 |

0.170

<0.001

<0.001

Table 2. Factors Associated with Guideline Compliance based on the Logistic Regression

| Variable | OR* | 95% C.I. | | P-value |
|----------------------------|-------|----------|--------|---------|
| Age Groups | | | | |
| 50-64 | 1.897 | 0.851 | 4.228 | 0.027 |
| 65-74 | 3.316 | 1.322 | 8.320 | |
| >75 | 1.730 | 0.661 | 4.528 | |
| 20-49 | Ref | | | |
| Stage | | | | |
| Stage IA IB with Grade 1 | 0.151 | 0.022 | 1.020 | <0.001 |
| Stage IA-IIIIB | 0.323 | 0.198 | 0.526 | |
| Stage IIIC-IV | Ref | | | |
| Grade | | | | |
| Grade 2 | 0.421 | 0.093 | 1.898 | 0.071 |
| Grade 3 | 0.548 | 0.128 | 2.351 | |
| Grade 4 | 0.529 | 0.119 | 2.358 | |
| Unknown | 0.212 | 0.045 | 0.990 | |
| Grade1 | Ref | | | |
| Charlson Comorbidity Index | | | | |
| 1 | 1.188 | 0.675 | 2.090 | 0.171 |
| 2 | 0.731 | 0.267 | 1.999 | |
| 3+ | 3.803 | 0.710 | 20.356 | |
| Unknown | 0.544 | 0.263 | 1.128 | |
| 0 | Ref | | | |
| Tertiary | | | | |
| Tertiary Hospital | 1.921 | 1.104 | 3.341 | 0.021 |
| Non Tertiary Hospital | Ref | | | |

Table 2. (continued)

| Income Level | | | | |
|---|-------|-------|--------|-------|
| Low | 1.014 | 0.362 | 2.834 | 0.956 |
| Moderate | 1.000 | 0.339 | 2.955 | |
| High | 1.188 | 0.539 | 2.615 | |
| Very High | Ref | | | |
| Insurance Status | | | | |
| Medicaid | 0.311 | 0.125 | 0.774 | 0.003 |
| Medicare | 0.312 | 0.148 | 0.659 | |
| Private Insured | Ref | | | |
| Appalachian Residence and Metropolitan Status | | | | |
| Appalachian Metro Area | 5.069 | 0.890 | 28.876 | 0.166 |
| Non Appalachian Metro Area | 1.325 | 0.480 | 3.662 | |
| Non Appalachian Rural Area | 0.847 | 0.356 | 2.016 | |
| Appalachian Rural Area | Ref | | | |
| *OR, Odds Ratio | | | | |

Table 3. Factors Associated with Survival from the Cox Regression Model

| Variable | 95% C.I. | | | P-value |
|----------------------------|----------|-------|-------|---------|
| Age Groups | | | | |
| 50-64 | 1.732 | 1.028 | 2.919 | 0.043 |
| 65-74 | 1.732 | 0.974 | 3.082 | |
| >75 | 2.316 | 1.256 | 4.271 | |
| 20-49 | Ref | | | |
| Stage | | | | |
| Stage I | 0.090 | 0.054 | 0.151 | <0.001 |
| Stage II | 0.185 | 0.108 | 0.315 | |
| Stage III | 0.653 | 0.480 | 0.888 | |
| Stage IV | Ref | | | |
| Grade | | | | |
| Grade | | | | 0.325 |
| Grade 2 | 1.114 | 0.477 | 2.604 | |
| Grade 3 | 1.329 | 0.599 | 2.946 | |
| Grade 4 | 1.251 | 0.553 | 2.830 | |
| Unknown | 0.831 | 0.341 | 2.026 | |
| Grade1 | Ref | | | |
| Charlson Comorbidity Index | | | | |
| 1 | 1.101 | 0.794 | 1.528 | 0.323 |
| 2 | 1.575 | 0.868 | 2.859 | |
| 3+ | 2.458 | 1.200 | 5.033 | |
| Unknown | 1.506 | 0.970 | 2.339 | |
| 0 | Ref | | | |
| Tertiary | | | | |
| Tertiary Hospital | 1.034 | 0.765 | 1.397 | 0.830 |
| Non Tertiary Hospital | Ref | | | |

Table 3. (continued)

| Insurance Status | | | | |
|---|-------|-------|-------|-------|
| Medicaid | 1.340 | 0.773 | 2.323 | 0.510 |
| Medicare | 1.188 | 0.780 | 1.809 | |
| Private Insured | Ref | | | |
| Appalachian Residence and Metropolitan Status | | | | |
| Appalachian Metro Area | 0.876 | 0.440 | 1.742 | 0.194 |
| Non Appalachian Metro Area | 0.698 | 0.491 | 0.990 | |
| Non Appalachian Rural Area | 0.742 | 0.497 | 1.108 | |
| Appalachian Rural Area | Ref | | | |
| GCD to Closest Tertiary Hospital | 1.003 | 1.000 | 1.006 | 0.094 |
| Guideline Adherence | | | | |
| NCCN Guideline Non Adherent | 1.615 | 1.111 | 2.347 | 0.012 |
| NCCN Guideline Adherent | Ref | | | |
| *HR, Hazard Ratio | | | | |

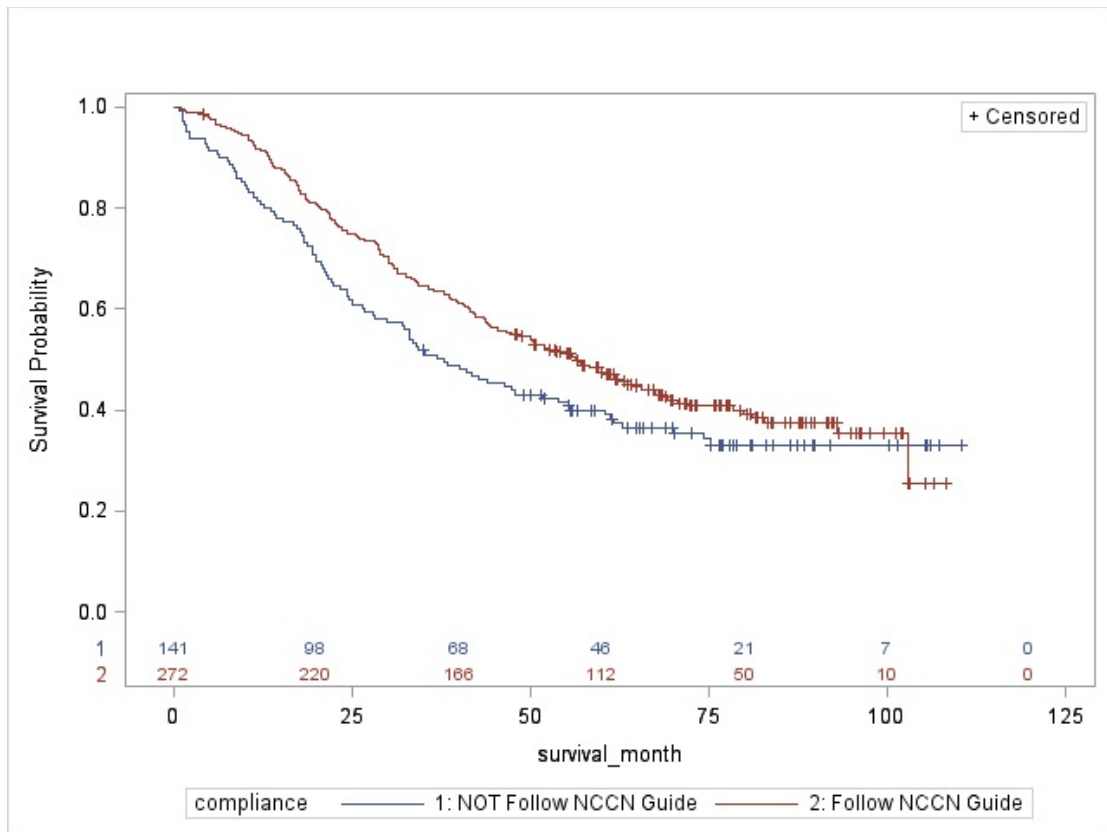


Figure 1. Kaplan Meier Plots for Ovarian Cancer Patient Survival by Compliance Status

DISCUSSION

Ovarian cancer remains a significant cause of cancer death for women. One way to improve cancer outcomes is to ensure that women have access to expert-recommended care. Cancer incidence rates in Kentucky are among the highest in the United States, and the geographical region of Central Appalachia has numerous barriers that may limit access to expert medical care. Understanding the specific disparities is critical to improving ovarian cancer outcomes in this region.

The age adjusted incidence for ovarian cancer in the state of Kentucky in 2013-2014 was 10 cases per 100,000 people, similar to the national rate of 11.9 cases per 100,000 people (12). The corresponding age-adjusted mortality rate is 6.8 per 100,000 in Kentucky versus 7.2 per 100,000 nationwide (12). Compliance rates for NCCN-recommended treatment for ovarian cancer have not been previously reported for the state of Kentucky or Central Appalachia.

In this investigation, the overall NCCN compliance rate for the treatment of ovarian cancer was 65%. As reported in other studies, women who received guideline-compliant care had better overall survival. In our multivariate analysis, younger women (20-49 years) were significantly less likely to receive guideline recommended ovarian cancer treatment compared to age 65-74 years. Previous publications have reported that older women are at risk of receiving NCCN non-compliant care for ovarian cancer (7) (13) (14) (8) , but our findings are the first show this disparity in younger women. This is particularly poignant when considering the potential number of life-years at risk for young women diagnosed with cancer. When using Medicare-linked databases,

population-based reports are restricted to age 65 years or older (8). In our investigation, we were able to include all women age 20 years or older.

We elected to analyze age as a categorical as opposed to a continuous variable. This is logical as expert organization guidelines directing management of adnexal masses vary for premenopausal versus postmenopausal women (15). Furthermore, age related comorbidities are likely to be a greater factor in elderly women, as opposed to those who have just gone through menopause. Consequently, utilizing three age strata (20-49, 65-74, >75) considers age in relation to these key factors, as opposed to consideration of age as a continuous variable. The results of our survival analysis demonstrate that younger age is associated with better survival; which is an expected result. The results of our logistic regression, demonstrate that younger age is associated with inferior guideline compliance, which is unexpected. This may suggest that decision-making guidelines in the younger than 50 years age group are not satisfactory.

Other publications have demonstrated low rates of NCCN guideline compliance for early stage cancers (6) (13). We also find that women with early stage ovarian cancer are less likely to receive NCCN-compliant care. As young women are more likely to have early stage disease (16), it is possible that stage and age are confounding factors in these analyses. Patients with early stage ovarian cancer are more likely to have appropriate staging and treatment when their initial surgery is performed by a gynecologic oncologist (17), so referral to a specialist is an important consideration.

In our study, patients with private insurance were more likely to receive guideline-compliant treatment than those with Medicaid or Medicare. This relationship between insurance provider and quality of care in ovarian cancer has been previously

reported (14). It is not well understood why the type of insurance impacts the quality of treatment, though possible explanations include differences in physician reimbursement, cultural issues relating to access, or the possibility that insurance type may be a surrogate variable for socioeconomic status. It is important to note that in this investigation, patient education and income status were not associated with differences in NCCN-compliance or with overall survival.

NCCN guideline compliance was higher when treatment was provided at a tertiary care facility. It is well known that for the treatment of ovarian cancer, high volume hospitals, and experienced surgeons provide more guideline-concordant care (2). In addition, a recent report demonstrated greater rates of concordance when care was provided at NCI-designated Comprehensive Cancer Centers (CCC), compared to both high and low volume hospitals that were not NCI-designated CCC hospitals (5).

Other publications on ovarian cancer treatment have commented on disparities in guideline concordance based on socioeconomic status and race (18). No race disparate care was noted in our analysis, but the evaluation is limited by small numbers of African Americans in Central Appalachia (1.9%) and the state of Kentucky (7.9%). Insurance type may have served as a surrogate variable for socioeconomic status, as income levels are based upon census tract data in relationship to a subject's zip code of residence, while Medicaid insurance status is linked to low income on an individual level. We did observe a survival difference favoring non-Appalachian metropolitan populations compared to rural Appalachian populations. It is not evident whether this is related to the quality of care or other factors. Increased cancer mortality for Appalachian populations is a

relationship previously accredited to several factors including, medical comorbidities and access to care (19).

The literature is replete with guidelines and strategies for the preoperative evaluation of an ovarian mass; nevertheless, disparate cancer treatment remains commonplace. Many women are still not referred to a gynecologic oncologist for their initial ovarian cancer operation (17) (3). Ultrasound is available worldwide as a reliable and objective method to evaluate ovarian tumors (20) (21). Serial sonography further enhances ultrasound's ability to differentiate benign from malignant ovarian tumors (22) (23). In addition, multivariate index assays are highly sensitive in detecting malignancy (24) (25) (26) (27) including early stage cancers (28), and can be combined with ultrasound to further stratify the likelihood of malignancy (29). These practical preoperative evaluation strategies should be considered for all women whose ovarian tumors are concerning enough to require surgery, regardless of cancer stage, patient age, location, or insurance provider.

The authors acknowledge several study limitations. Claims data allowed us to determine whether or not chemotherapy was received, but we were unable to determine individual agents or number of cycles. We were also unable to determine the subspecialty or case volume of the primary surgeon, both of which have been associated with survival in other studies (14) (2). Lastly, our survival analysis did not include parameters related to the extent of primary cytoreduction, or parameters related to disease recurrence, including time to recurrence, and specific chemotherapy agents administered.

Our study has the following strengths. Our team linked KCR data to the majority of insurance databases our state, thereby minimizing insurance provider related biases.

Such biases are potentially significant in regards to age (Medicare – age over 65), and in regards to socioeconomic status (public versus private insurance in relation to patient income level). Our study gave a thorough account of medical comorbidities, a significant confounding variable that impacts decisions related to surgery and chemotherapy. The requirement for 13 months of continuous claims data mandated the exclusion of a substantial number of cases, but enabled us to capitalize on features of our KCR-insurance provider linked database. Lastly, we were able to use this comprehensive database to investigate patterns of care for ovarian cancer in Central Appalachia, an underserved and understudied region of the United States.

The findings of this investigation reaffirm that ovarian cancer survival is highest when treatment is concordant with published NCCN guidelines. Women with early stage disease, non-private insurance, or treatment at non-tertiary care hospitals are more likely to receive non-compliant care. We also report that younger women with ovarian cancer are significantly less likely to receive NCCN compliant care. Continued patient and physician education is needed to ensure that available imaging and biomarker tests are routinely used to help identify high risk women for referral to an ovarian cancer specialist, regardless of cancer stage, location, insurance provider, or patient age.

CONFLICT OF INTEREST STATEMENT

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